SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY
ASSAY ONLY TEMPLATE

A. 510(k) Number:

k103325

B. Purpose for Submission:

New device

C. Measurand:

Intact Parathyroid Hormone (PTH)

D. Type of Test:

Quantitative, Chemiluminescent Magnetic Particle Immunoassay

E. Applicant:

Immunodiagnostic Systems Ltd

F. Proprietary and Established Names:

1. IDS-iSYS Intact PTH
2. IDS-iSYS Intact PTH Control Set
3. IDS-iSYS Intact PTH Calibrator
4. The IDS-iSYS Intact PTH Calibration Verifiers

G. Regulatory Information:

Product Code	Classification	Regulation Section	Panel
CEW	Class II	21 CFR 862.1545 Parathyroid Hormone Test System	Clinical Chemistry (75)
JIT	Class II	21 CFR 862.1150 Calibrator	Clinical Chemistry (75)
JJX	Class I, reserved	21 CFR 862.1660 Quality Control Material	Clinical Chemistry (75)

H. Intended Use:

1. Intended use(s):

Refer to indication for use below

2. Indication(s) for use:

   The IDS-iSYS Intact PTH assay is intended for the quantitative determination of PTH in human serum or plasma on the IDS-iSYS Multi-Discipline Automated Analyzer. Results are to be used in the differential diagnosis of hypercalcemia and hypocalcemia resulting from disorders of calcium metabolism

   The kit is for in vitro diagnostic use only.

   The IDS-iSYS Intact PTH assay Control Set is intended for use as assayed quality control samples to monitor the precision of the IDS-iSYS Intact PTH assay.

   The IDS-iSYS Intact PTH Calibrator is intended for the calibration of the IDS-iSYS Intact PTH assay.

   The IDS-iSYS iPTH Calibration Verifier is intended for verification of calibration of the IDS-iSYS iPTH Assay when performed on the IDS-iSYS Multi-Discipline Automated Analyzer.

3. Special conditions for use statement(s):

   For *in vitro* diagnostic use only

4. Special instrument requirements:

   IDS-iSYS Multi-Discipline Automated Analyzer

   All performance data was generated on the IDS-iSYS Multi-Discipline Automated Analyzer

I. Device Description:

1. IDS-iSYS Intact PTH Kit Contents:
   a. Reagent Cartridge
      i. Magnetic particles coated with streptavidin in a phosphate buffer containing sodium azide as preservative (<0.1%), 1 bottle, 2.7 mL.
      ii. Anti-PTH labeled with an acridinium ester derivative, in buffer containing goat serum with sodium azide as preservative (<0.1%), 1 bottle, 7.25 mL.
      iii. Anti-PTH labeled with biotin, in buffer containing bovine and goat proteins with sodium azide as preservative (<0.1%), 1 bottle, 13 mL.
   b. IDS-iSYS Intact PTH Calibrators
      i. Calibrators A and B; a buffered porcine serum matrix containing PTH and sodium azide as preservative (<0.2%), 2 each of 2 concentration levels, 1 mL.

2. IDS-iSYS Intact PTH Control Set Contents:
    a. 3 Controls; a buffered porcine serum matrix containing PTH (1.84) and sodium azide as preservative (<0.2%, w/w), 6 each of 3 concentration levels, 1.0 mL.

3. The IDS-iSYS Intact PTH Calibration Verifiers:
    a. 2 each of 5 controls (2 mL for level 0, 1mL for levels 1 - 4) of human recombinant PTH (1-84) in buffered porcine serum with <0.2% w/w sodium azide preservative (<0.1% reconstituted).

All human source materials were tested by FDA approved methods and found to be negative for HIV ½, HBsAg, and HCV.

J. Substantial Equivalence Information:

1. Predicate device name(s):

    Roche Diagnostics Elecsys PTH Test System

2. Predicate 510(k) number(s):

    k070709

3. Comparison with predicate:

Items	IDS-iSYS Intact PTH assay (Candidate Device)	Roche Elecsys PTH assay (Predicate Device)
Similarity		
Intended Use	Same	For the *in vitro* diagnostic use in the quantitative determination of intact parathyroid hormone (PTH) in plasma or serum.
Test Principle	Same	Chemiluminescence Immunoassay
Calibration	Same	New lot or after 7 days
Quality Control	Same	3 levels
Calibrators	Same	2 levels
Difference		
Sample	Serum/SST/EDTA Plasma	Serum/K3-EDTA Plasma
Antibody Types	Both polyclonal	Both monoclonal
Assay Kit Components	Reagent pack with calibrators	Reagent packs and iPTH master control curve
Detection limits	LoB = 1.3 pg/mL LoD = 2.6 pg/mL LoQ = 4.6 pg/mL	1.2 pg/mL
Precision	Within-run % CV = 6 Total % CV = 8	Within-run % CV = <5 Total % CV = <7
Normal Range	11.5 – 78.4 pg/mL	15 - 65 pg/mL

Measuring Range	5 – 5000 pg/mL	1.2 – 5000 pg/mL
Hook Effect	> 95,000 pg/mL	17,000 pg/mL

K. Standard/Guidance Document Referenced (if applicable):

- CLSI Guideline EP5-A2: Evaluation of Precision Performance of Qualitative Measurement Methods
- CLSI Guideline EP6-A: Evaluation of the Linearity of Qualitative Measurement Methods
- CLSI Guideline EP7-A2: Interference Testing in Clinical Chemistry
- CLSI Guideline EP9-A2: Method Comparison and Bias Estimation Using Patient Samples
- CLSI Guideline EP17-A: Protocols for Determination of Limits of Detection and Limits of Quantitation
- CLSI C28-A3: Defining, Establishing, and Verifying Reference Intervals in the Clinical Laboratory; Approved Guideline - Third Edition.
- CEN 13640: Stability Testing of In Vitro Diagnostic Reagents

L. Test Principle:

A chemiluminescent immunoassay technique is used, in which a polyclonal goat anti-human antibody recognizing the C-terminal region (amino acids 39-84) of human PTH is used as the capture antibody. A polyclonal goat anti-human PTH antibody which recognizes the N-terminal region (amino acids1-84) of PTH, is conjugated with acridinium for detection. This system also detects the large PTH fragment of amino acid 7-84. Patient samples are incubated with both antibodies followed by the addition of streptavidin coated magnetic particles with further incubation. A magnet is then used to capture the labeled antibody-antigen complexes, and following a wash and the addition of reagent, the concentration of PTH is determined. Concentration of PTH is directly proportional the amount of emitted light from the acridinium labels.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Precision was evaluated following CLSI guideline EP5-A2. Two replicates of each of 10 samples, 7 plasma (K-EDTA) samples (4 spiked with high PTH calibrator) and 3 serum samples (2 spiked with high PTH calibrator), were tested twice a day on 20 separate days, yielding 80 replicates total over 40 assays.

Precision Results

	Units = pg/mL							
		Within-run		**Within-day**		**Total**		
Sample	**Mean PTH Conc.**	**SD**	**CV**	**SD**	**CV**	**SD**	**CV**	**No. Observ.** / **No. Days**

Sample	Units = pg/mL							No. Observ.	No. Days
	Mean PTH Conc.	Within-run		Within-day		Total			
		SD	CV	SD	CV	SD	CV		
Plasma	13.3	80	0.6%	0.8	5.9%	1.0	7.4%	80	20
Serum	21.0	80	1.3%	0.8	3.6%	1.7	8.2%	80	20
Plasma	29.0	80	1.1%	1.1	3.9%	1.7	5.8%	80	20
Plasma	41.1	80	1.1%	1.8	4.3%	2.2	5.4%	80	20
Serum Spiked	192	80	4%	7	3.6%	10	5.1%	80	20
Plasma Spiked	223	80	2%	7	3.2%	9	4.1%	80	20
Plasma Spiked	740	80	7%	30	4.1%	35	4.7%	80	20
Plasma Spiked	1956	80	35%	69	3.5%	87	4.4%	80	20
Plasma Spiked	2599	80	59%	105	4.0%	124	4.8%	80	20
Serum Spiked	3807	80	52%	160	4.2%	191	5.0%	80	20

b. Linearity/assay reportable range:

Study Protocol:
Linearity was evaluated following CLSI guideline EP6-A. Plasma pool samples were used for the study. High spiked pool samples were diluted using low pool samples to give a total of 9 intermediate dilutions. All samples were tested in duplicate and ranged from 4.4 pg/mL to 5434 pg/mL. The average dilutions recovery was 101.4%. Linear regression generated the following regression: $y = 1.002x - 4.748$, $R = 1.00$.

Based on the linearity results, the sponsor claimed that the assay is linear across the entire claimed measuring range (5 – 5000 pg/mL).

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

Traceability:

The IDS-iSYS Intact PTH calibrators, controls and calibration verifiers are traceable to in-house reference calibrators, produced from PTH purchased from a commercial source and a matrix of 75% porcine serum and 25% MOPS-BSA buffer. Reference calibrators are produced by gravimetric addition of synthetic PTH to the matrix and are compared to a FDA cleared assay.

Stability:

Real-time and accelerated testing was conducted. The stability study protocol and the acceptance criteria have been reviewed and found to be acceptable. The sponsor stated acceptance criteria for all stability studies was <10% difference from the day 0 value. The results support the stability claims summarized in the below table.

Close-Vial and Open-Vial Stability

Item	Storage Conditions	Claimed

			Stability
Reagent Packs	Close-Vial	2-8°C	6 months
	Open-Vial	On system	21 days
	Open-Vial	2-8°C	28 days
Calibrators	Close-Vial	2-8°C	6 months
	Open-Reconstituted	-20°C	14 days
	Open-Reconstituted	On system	2 hours
Controls	Close-Vial	2-8°C	6 months
	Open-Reconstituted	-20°C	14 days
	Open-Reconstituted	On system	2 hours
Calibration Verifiers	Close-Vial	2-8°C	6 months
	Open-Reconstituted	On system	2.5 hours

Calibration Interval:

Stability across a 7 day calibration interval was assessed by calculating the percentage bias of the control samples on each day from the result obtained for that control samples from the calibration on the first day. The results support the product claim of a 7-day calibration interval.

Value Assignment:

- Calibrators: The in-house reference calibrators, which values have been assigned to correlate to the predicate device, were used to generate the master calibration curve. Value assignment of kit calibrators is lot-specific and is obtained by assaying the new calibrator sets as unknowns, run in duplicate in a minimum of at least 25 runs on one analyzer. The values obtained are verified by running three assays on three other analyzers with controls of known levels. Value assignment protocol states that the kit calibrators must fall within the specified ranges of 10.0 – 16.0 pg/mL for Calibrator A, and 3150.0 – 3850.0 pg/mL for Calibrator B.
- Controls: Value assignment of kit controls is lot specific and occurs through triplicate analysis in a minimum of 12 runs on a total of at least three analyzers. The assigned range is then calculated as the mean ± 3 standard deviations based on a nominal %CV of 10%, 7%, and 7% for kit controls 1, 2 and 3, respectively. The kit controls have the following acceptable ranges: 13.4 – 24.9 pg/mL for control 1, 139 – 213 pg/mL for control 2, and 1529 – 2343 pg/mL for control 3.
- Calibrator Verifiers: Value assignment of calibration verifiers is lot-specific and occurs through triplicate analysis in a minimum of 12 runs on a total of at least three analyzers. The assigned range is then calculated as the mean ± 3 standard deviations. The calibration verifiers have the following acceptable ranges: <LOQ – <LOQ

pg/mL for Cal Ver 0, 21.3 – 28.8 pg/mL for Cal Ver 1, 425 – 575 pg/mL for Cal Ver 2, 2125 – 2875 pg/mL for Cal Ver 3, and 3187 – 4312 pg/mL Cal Ver 4.

d. Detection limit:

Study Protocol:

Limit of Blank (LoB), Limit of Detection (LoD) and Limit of Quantitation (LoQ) were determined following guideline EP17-A.

For LoB determination, 10 replicates of the zero calibrator were performed over multiple 10 assay runs, over 10 operator days, using 2 analyzers and one reagent lot – giving 100 determinations in total.

For LoD determination, duplicates of each of seven patient samples were run with eight assays over eight days using one reagent lot – giving 112 determinations in total. The seven LoD samples were made by diluting an endogenous patient pool in the zero calibrator to give estimated PTH concentrations ranging from the LoB to 4xLoB.

For LoQ determination, duplicates of each of seven patient samples were run with eight assays over eight days using one reagent lot – giving 111 determinations in total (one measurement was lost to machine pipetting error). The seven patient samples were the same used for the LoD study. The level of imprecision used to accept the LoQ was less than 20%.

Result Summary:

Based on the study result, the following detection limit claims were made:

LoB	LoD	LoQ
1.2 pg/mL	2.5 pg/mL	4.5 pg/mL

The measuring range of the assay is 5 to 5000 pg/mL.

e. Analytical specificity:

- Interference

  Study Protocol:
  The sponsor evaluated the effect of the interfering substances using two patient serum pools with endogenous PTH at approximately 100-150 pg/mL and at 200 pg/mL. For each substance, two aliquots of this pool were thawed, one spiked with the test substance up to the maximum level shown below, and the other spiked with the zero calibrator (control). Interference was defined by the sponsor as ≤ 10% difference from the control sample. The PTH results (mean of 26 replicates) of the paired pools were compared to the control value and % interference was calculated using the following equation:

$$\% \text{ Interference} = \frac{(\text{Mean of spiked interferent value}) - (\text{Mean of control value})}{\text{Mean of control value}} \times 100$$

Samples were obtained containing either Human anti-mouse antibody (HAMA) or 1500 IU/mL Rheumatoid factor (RF). For each substance, two aliquots were made, one spiked with PTH and the other spiked with the zero calibrator (control). Acceptance criterion was a mean recovery of 85 – 115%, and was calculated using the following equation:

$$\% \text{ Recovery} = \frac{(\text{Mean of spiked PTH value}) - (\text{Mean of control value})}{\text{Expected PTH value}} \times 100$$

Result Summary:
Based on the sponsor-defined interference limit of ± 10%, the following claims were made:

- ❖ The below compounds at the indicated concentration do not cause significant interference with the assay.

Compound	Concentration up to
Bilirubin (unconjugated)	20 mg/dL
Biotin	300 nM
Hemoglobin	250 mg/dL
Triglycerides	3000 mg/dL
HAMA	1000 ng/mL
RF	1500 IU/mL

The sponsor states the following limitations in their labeling:

"Do not use hemolyzed samples. Hemolyzed samples may cause erroneous results."

- Cross-Reactivity

Study Protocol:
The sponsor evaluated cross-reactivity by using the zero calibrator as the test matrix. Each cross-reactant was assayed in duplicate with the corresponding control. The % Cross-reactivity was calculated using the following the equation:

$$\% \text{ Cross-reactivity} = \frac{\text{Mean iPTH of the Cross-Reactant pool}}{\text{Concentration of Cross-Reactant}} \times 100$$

Result Summary:
Based on the study results, all of the tested substances (except PTH 7-84) at the indicated concentration would not cross react significantly (<10%) with the proposed assay.

Cross-reactant Tested	Concentration Tested	% Cross-reactivity
Human Calcitonin	10,000 pg/mL	4
ß-Cross laps (CTX-1)	12 ng/mL	2
Osteocalcin	400 ng/mL	2
PTH 1–34	750 pg/mL	0.5
PTH 39–84	100,000 pg/mL	NA*
PTH 44–68	100,000 pg/mL	2
PTH 53–84	100,000 pg/mL	4
PTH 7-84	1,800 pg/mL	60

*NA = Not Applicable. Concentration was below the measuring range of the test.

f. Assay cut-off:

Not applicable.

2. Comparison studies:

a. Method comparison with predicate device:

Study Protocol:
A total of 158 random patient plasma (K-EDTA) samples from a clinical site were used in the method comparison studies. To cover the upper measuring range of the proposed iPTH assay, 13 patient samples were spiked with different amounts of high level PTH calibrator. Samples tested ranged from 6.2 pg/mL to 4553 pg/mL. Linear regression analysis was performed between the candidate device (IDS-iSYS system) and the predicate device (Roche Elecsys PTH).

Result Summary:
Linear Regression analysis yielded the equation $y = 1.06x – 3.78$, with an r^2 value of 1.00.

Conclusion:
Based on the regression analysis result, the sponsor claimed equivalency to the predicate assay.

b. Matrix comparison:

Study Protocol:

The matrix effect of various blood collection tubes on fresh and stored serum or plasma samples were evaluated. 50 mL of whole blood was collected into plain tubes, which were immediately spiked with various amounts of high PTH calibrator. Spiked whole blood was then immediately split into matched sample tubes and the samples were

immediately processed and analyzed using the Intact PTH kit. The following tube types were evaluated: Serum, Serum Separator Tubes and K-EDTA plasma. The sponsor's definition of equivalent performance is no more than 10% difference between each tube type compared to the EDTA plasma. The samples tested had values ranging from 33 to 3200 pg/mL.

Differences in PTH values (mean of duplicate determinations) between tube types on freshly processed samples were evaluated using Bias plots and correlation graphs.

To evaluate the effect of various storage conditions on PTH, % Difference was calculated using the following equation:

$$\% \text{ Difference} = \frac{\text{Test Condition - Baseline Condition}}{\text{Baseline Condition}} \times 100$$

Result Summary:

Tube Y	Tube X	Slope	Intercept	r^2
Serum	EDTA plasma	0.9924	0.14	0.9995
Serum Separator	EDTA plasma	1.0048	-0.16	0.9996

Conclusion: Based on the study results, the sponsor claims the use of EDTA plasma tubes, Serum tubes and Serum Separator tubes.

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable

b. Clinical specificity:

Not applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The reference interval was assessed from 243 serum samples from healthy adults (age 32 – 68, 136 female and 104 male) with normal Calcium, Creatinine and Vitamin D values

(> 10 ng/mL). The samples were obtained from a commercial source. Ethnicity was 75% Caucasian and 25% African American and Hispanic. All samples were negative or non-reactive for HBaAg, HCV, RPR, HIV1&2 and HIVAg by FDA approved methods. Samples were assayed in duplicate, using one reagent batch on one instrument. These data provided the central 95 % Reference Interval (apparently healthy adults) of: 11.5 to 78.4 pg/mL.

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.